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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/511,731 | 10/18/2004 | Maria L. Garcia | 21092YP | 2580 |
| 210 | 7590 | 01/23/2007 | | |
| MERCK AND CO., INC P O BOX 2000 RAHWAY, NJ 07065-0907 | | | EXAMINER GRAZIER, NYEEMAH | |
| | | | ART UNIT | PAPER NUMBER |
| | | | 1626 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|--|------------|---------------|
| 3 MONTHS | 01/23/2007 | PAPER |

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/511,731

Applicant(s)

GARCIA ET AL.

Examiner

Nyeemah Grazier

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 February 2005.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) 6-17 and 19-21 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5 and 18 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 2/16/05.
- 4) ☒ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____.

DETAILED ACTION
FIRST ACTION ON THE MERITS

I. ACTION SUMMARY

Claims 1-21 are currently pending. Claims 6-17, and 19-21 are withdrawn from further consideration by the Examiner because said claims are drawn to a non-elected invention. 37 C.F.R. § 1.142(b).

II. PRIORITY

This application is a 371 of PCT/US03/18842, filed June 13, 2003; which claims benefit of US Provisional Application 60/389,222, filed June 17, 2002.

III. INFORMATION DISCLOSURE STATEMENT

The information disclosure statement (IDS) submitted on February 16, 2005 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

IV. RESTRICTION/ELECTION

The Markush group set forth in the claims includes both independent and distinct inventions, and patentable distinct compounds or species within each invention. However, the instant application discloses and claims a plurality of patentable distinct inventions far too numerous to list individually. Moreover, each of these inventions contain a plurality of patentable distinct compounds, also far too numerous to list individually. Restriction to one of the following Inventions is required pursuant to 35 U.S.C. § 121, wherein an Invention is a set of patentable distinct inventions of a broad statutory category.

- I. Claims 1-5, and 18, drawn to the compounds and compositions, classified in class 548, subclass 417, and class 514, subclass 410, for example.

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- II. Claims 6-17, drawn to the method of treatment, classified in class 514, subclass 410, for example.
- III. Claims 19-21, drawn to the process of manufacturing, classified in 548, subclass 417, for example.

Markush Claims

A provisional election of a species is required because the Markush-type claims of the instant application include distinct independent inventions. Restriction of a Markush group is proper where the compounds within the group either (1) do not share a common utility, or (2) do not share a substantial structural feature disclosed as being essential to that utility. See In re Harnisch, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); See also Ex Parte Hozumi, 3 USPQ2d 1059 (BPAI 1984). Absent evidence that subject matter of the Markush-type claim lacks unity of invention, the Office may not merely "refuse to examine that which applicants regard as their invention." See M.P.E.P. § 803.02; In re Harnish, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and Ex parte Hozumi, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility. Additionally, a Markush group may encompass a plurality of independent and distinct inventions where two or more members are so unrelated and diverse that a prior art reference anticipating the claim with respect to one of the members would not render the other member(s) obvious under 35 U.S.C. §103. **Therefore, in addition to an election of one of the abovementioned Inventions, restriction is further required under 35 U.S.C. § 121.**

Upon election of an invention, election of a single species is further required, including an exact definition of each substitution on the base molecule, (i.e., Formula (I)), wherein a single member at each substituent group or moiety is selected. For example, if a base molecule has a substituent group R3 and X, wherein R3 is recited to be any one of hydrogen, aryl, arylalkyl, or arylalkenyl, and X is O or S, etc., then applicant must select a single substituent for R3 or X. For instance: R3 is methyl and X is O. This process is repeated for each variable so that a single compound is identified.

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In the instant case, upon election of a single compound, the Office will review the claims and disclosure to determine the scope of the independent invention encompassing the elected compound. The elected compounds should be similar that they will encompass the same inventive concept and reduction to practice. The scope of an independent invention will encompass all compounds within the scope of the claim, which fall into the same class and subclass as the elected compound, but may also include additional compounds, which fall in related subclasses. Examination will then proceed on the elected compound and the entire scope of the invention encompassing the elected compound as defined by common classification.

A clear statement of the examined invention, defined by those class(es) and subclass(es) will be set forth in the first action on the merits. Note that the restriction requirement will not be made final until such time as applicant is informed of the full scope of compounds along with (if appropriate) the process of using or making said compound under examination. This will be set forth by reference to specific class(es) and subclass(es) examined. Should applicant traverse on the ground that the compound are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the compound to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

All compounds falling outside the class(es) and subclass(es) of the selected compound and any other subclass encompassed by the election above will be directed to nonelected subject matter and will be withdrawn from consideration under 35 U.S.C. 121 and 37 C.F.R. 1.142(b). Applicant may reserve the right to file divisional applications on the remaining subject matter. The provisions of 35 U.S.C. 121 apply with regard to double patenting covering divisional applications.

Applicant is reminded that upon cancellation of claims to a nonelected invention, the inventions must be amended in compliance with 37 C.F.R. 1.48(b) if one of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 C.F.R. 1.48(b) and by the fee required under 37 C.F.R. 1.17(i).

Applicants can review the claims and disclosure to determine the scope of the invention and can set forth a group of compounds, which are so similar, within the same inventive concept and reduction to practice. Markush claims require sufficient support in the disclosure for each member of the Markush group. See MPEP § 608.01(p). Applicant should exercise caution in making a selection of a single member for each substituent group on the core structure as the selected species must be consistent with the written description.

Rationale Establishing Patentable Distinctiveness Within Each Group

Invention I and II are related as product and process of use of the product. However, the inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product M.P.E.P. § 806.05. In the instant case, the process of treating ocular hypertension may be accomplished with another materially distinct compound.

Invention I and III are unrelated processes. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects. (MPEP §§ 806.04, 808.01). In the instant case, process recited in claim 19, for example, uses a different method than the process in claim 21 (i.e. using *Aspergillus alliaceus*). Because these inventions are unrelated for the reasons given above and the search required for Group I is not required for Group III, restriction for examination purposes as indicated is proper. Absent restriction, the examination of the instant application would impose a serious burden.

Additionally, because of the plethora of classes and subclasses in each of the Inventions, a serious burden is imposed on the examiner to perform a complete search of the defined areas. Lack of restriction would impose a serious burden on the Examiner. Thus, based on the abovementioned rationale, the restriction as set forth in the instant application is proper.

In sum, each Group listed above has a diverse chemical structure, different chemical properties, different modes of action, and different effects and reactive conditions and is therefore recognized in the art as being distinct from one another. MPEP §§ 806.04, 808.01. Additionally, the level of skill in the art is not such that one invention would be obvious over the

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other invention (Group), i.e. they are patentable over each other. Chemical structures, which are similar, are presumed to function similarly, whereas chemical structures that are not similar are not presumed to function similarly. The rebuttable presumption, that similar chemical structures behave similarly, may be overcome by scientific reasoning or evidence showing that the structure of the prior art would not have been expected to function as the structure of the claimed invention. Note that in accordance with the holding of Application of Papesch, 50 CCPA 1084, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) and In re Lalu, 223 USPQ 1257 (Fed. Cir. 1984), chemical structures are patentably distinct where the structures are either not structurally similar, or the prior art fails to suggest a function of a claimed compound would have been expected from a similar structure.

Advisory of Rejoinder

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

A. Election: Telephonic Inquiry

During a telephone conversation with Sylvia Ayler, Esquire on or about January 11, 2007, a provisional election was made with traverse to prosecute the invention of Group I, claims 1-5, and 18, directed to a product. Claims 6-17, and 19-21 are hereby withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Applicant is reminded that he/she is required to affirm this election when responding to this Office Action.

V. REJECTION(S)

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 5, and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by *Staub et al.*, New Paspalinine Derivatives with Antiinsectan Activity From the Sclerotia of *Aspergillus Nomius*, Tetrahedron Letters, vol. 34, No. 16, pp. 2569-2572, 1993. The prior art of record teaches the instant invention wherein R1, R1a, R3, R2, and R7 are each hydrogen atoms; “b” is a double bond; R5 is –OH, and wherein R4 is H or –C(O)–(CH₂)_n–CH(N(R6)2)–R8 where n is 0, R8 is CH(CH₃)₂. See, Staub et al., at p. 2570, compounds 3 and 4. *See also*, Laakso, et al., US 5,227,396. Laakso, et al. discloses the abovementioned species of Formula (I) of the instant invention. See, e.g., Answer 23 of 61, HCAPLUS RN 151341-77-4, and 151341-78-5 (attached).

Dependent claims 3 and 4 are therefore rejected as being dependent upon a rejected based claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) that forms the basis for all obviousness rejections set forth in this Office action:

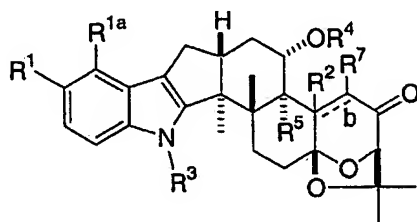
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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Graham v. John Deere Co. set forth the factual inquiries necessary to determine obviousness under 35 U.S.C. §103(a). See *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Specifically, the analysis must employ the following factual inquiries:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 3 and 4 are rejected over Staub, et al., Tetrahedron Letters, vol. 34(16), pp. 2569-2572, 1993. The instant invention is drawn to the compounds and compositions of formula (I):

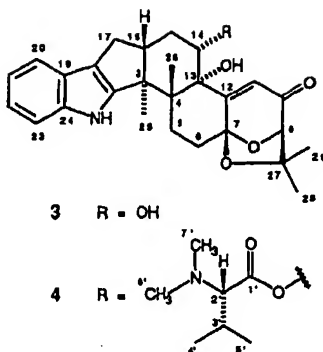


Wherein inter alia: R¹, R^{1a}, R³, R², and R⁷ are each hydrogen atoms; "b" is a double bond; R⁵ is -OH, and wherein R⁴ is H or -C(O)-(CH₂)_n-CH(N(R⁶))₂-R⁸.

The Scope and Content of the Prior Art (MPEP §2141.01)

The prior art of reference is drawn to paspalinine derivatives. Namely, compounds of formula (4) on p. 2570. See below.

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The Difference Between the Prior Art and the Claims (MPEP §2141.02)

The difference between the prior art of record and instant invention is that the instant invention of claims 3 and 4 R4 is $-\text{C}(\text{O})\text{CHN}(\text{R}_6)_2-(\text{CH}_2)_n-\text{CH}_3$ while the art of record is drawn to group R (compound 4). Thus the difference is the art is drawn to an isopropyl group, while the instant invention straight chain alkyl group (ethyl, propyl, butyl, etc.).

Resolving Level of Ordinary Skill in the Pertinent Art and Prima Facie Obviousness

The pertinent art is chemistry. Level of skill in the art is high. The motivation to make claimed compound derives from the expectation that structurally similar compounds are generally expected to have similar properties and have similar utilities. *In re Gyurik*, 596 F. 2d 1012, 201 USPQ 552 (CCPA 1979). Members of a homologous series must possess unexpected properties not possessed by the homologous compounds disclosed by the prior art. *In re Hass*, 60 USPQ 548 (CCPA 1944). Adjacent homologs are considered to be obvious absent unexpected results. *In re Henze*, 85 U.S.P.Q. 261, 263 (CCPA 1950).

VI. OBJECTION(S)

Specification

The abstract of the disclosure is objected to because page 2 of the specification appears to be missing text or contains a blank space. Correction is required. See MPEP § 608.01(b).

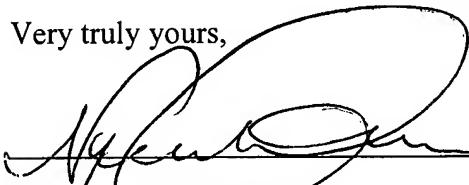
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VII. CONCLUSION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nyeemah Grazier whose telephone number is (571) 272-8781. The examiner can normally be reached on Monday through Thursday and every other Friday from 8:30 a.m. - 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane, can be reached on (571) 272 - 0699. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Very truly yours,


Nyeemah Grazier, Esq.

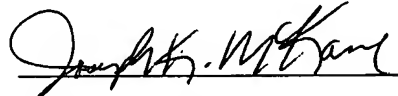
Patent Examiner, Art Unit 1626

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